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A transgenic animal can be defined as an organism that has undergone a stable modification of genotype as a result of genetic manipulation. Such animals are being increasingly employed as research and development tools by both academic and commercial institutions. The primary methods by which transgenic animals can be generated will be described. The relative merits of the approaches will be illustrated, as will their potential use in the discovery and development of novel therapeutic entities.

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Transgenic animals as tools in drug development

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Abstract

A transgenic animal can be defined as an organism that has undergone a stable modification of genotype as a result of genetic manipulation. Such animals are being increasingly employed as research and development tools by both academic and commercial institutions. The primary methods by which transgenic animals can be generated will be described. The relative merits of the approaches will be illustrated, as will their potential use in the discovery and development of novel therapeutic entities.

Introduction

The ability to manipulate the genotype of an animal has allowed a systematic investigation of a large number of fundamental biological phenomena in the context of the whole animal. The principal means by which transgenic animals are currently produced are pronuclear DNA microinjection, blastocyst microinjection of embryonic stem (ES) cells and replication-defective viral vector transduction (for a review see [1]).

The route chosen for a particular project will depend upon the type of biological question being addressed and the relative merits and limitations of the different methods. For example, while the ability to target specific regions of the genome in ES cells probably holds the most promise for the future, this technique is currently restricted to use in the mouse. In contrast, pronuclear microinjection has been employed in a number of different species, including commercially important animals such as the pig, goat, sheep and cattle. Viral vectors were the first means by which DNA was introduced into the germline; however, the technical limitations of this approach have restricted their use. In humans,

where gene therapy by somatic transformation is beginning to bear fruit, viral-mediated DNA transduction remains the predominant route [2].

The widespread use of transgenics has greatly aided our understanding in many areas of biology, including investigations of possible mediators involved in inflammation [3-5]. Briefly, other areas include: (i) the definition of *cis*-acting DNA sequences involved in tissue-specific, developmentally regulated gene expression, e.g. novel promoter/enhancer combinations and locus control regions; (ii) investigation of the consequences of ectopic gene expression, e.g. oncogenesis; (iii) new insights into the influence of genome organisation on gene expression, e.g. genomic imprinting; and (iv) the opportunity to study developmental processes as a result of the fortuitous (insertional mutagenesis), selected (promoter/enhancer trap transgenes) or defined (homologous recombination) genetic lesions that can be generated using these techniques [1].

In some cases these investigations have resulted, by design or fortuitously, in the production of novel rodent models of human disease states that should prove invaluable in gaining a better understanding

of the underlying dysfunction in their human counterpart. Future developments along these lines may result in many of the existing animal models being replaced by such "designer" transgenics. In addition to the extensive transgenic work being performed in rodents, several groups are trying to exploit these technologies in commercially important agricultural species. Initial attempts to generate significant improvements in animal performance, e.g. in growth rate, meat quality, or by adding value to milk through the production of human proteins, have produced mixed results.

Transgenic rodents are already being evaluated in the pharmaceutical industry, e.g. as a generic source of novel immortalised cell lines [6] and as a means of evaluating more effectively the *in vivo* toxicity and mode of action of mutagenic agents [7, 8]. The ability to "humanise" rodents provides a major opportunity to replace the existing animal models with more refined small animal models, which, in turn, could lead to a reduction in overall animal usage. It is anticipated that, in the pharmaceutical industry, transgenics will have an impact on both the discovery and development of novel therapeutic entities by facilitating target identification and validation, and the development of more refined generic animal models in which to evaluate candidate pharmaceuticals.

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Utility of firefly luciferase as a reporter gene for promoter activity in transgenic mice

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Photinus pyralis (firefly) luciferase assays are extremely rapid, inexpensive, very sensitive and utilize commercially available non-radioactive substrates. The luciferase assay is more sensitive than assaying chloramphenicol acetyltransferase expression when monitoring eukaryotic promoter activity in CV-1 cells (1).

We report the utility of the firefly luciferase gene to monitor promoter activity in transgenic mice. We cloned the luciferase gene downstream of a small DNA fragment of the chicken alpha-skeletal actin promoter. This fragment included the transcription start site and 200 base pairs of 5'-flanking sequences (2). The hybrid gene was used to generate transgenic mice expressing the luciferase gene product. By exploiting the fact that the mouse tail contains skeletal muscle, expression of luciferase by the skeletal muscle actin promoter could be measured non-invasively using tail biopsy samples. Tail biopsies were taken from 73 4-day-old F0-transgenic offspring. Sample preparations and luciferase measurements were as described (1). Table 1 shows that luciferase activity was detected in 10 (14%) of the neonates, and that animals could be classified as low, medium, and high luciferase expressors. The presence of the transgene in these animals was demonstrated by DNA dot-blot analysis (data not shown). Luciferase activity was not detected in control animals.

TABLE 1. Luciferase expression in transgenic mice.

Neonatal Mouse	Luciferase Activity ($\times 10^{-3}$)*
Control	0
Transgenic (low expression)	102, 139, 169
Transgenic (medium expression)	441, 636, 850, 1004, 1015
Transgenic (high expression)	15274, 15842

* Bioluminescence measurements were made in the Berthold Biolumat LB9505. Activity is reported as light units per 10 μ l of tail extract after subtracting background.

The luciferase assay allows immediate detection of F0-transgenic offspring that express the transgene. This is the first report on the expression of firefly luciferase in transgenic animals.

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